

M.H



The  
Patent  
Office

PCT/GB 99/03109

09787195

INVESTOR IN PEOPLE

GB 99/3109

EJU

**PRIORITY  
DOCUMENT**

SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17.1(a) OR (b)

The Patent Office  
Concept House  
Cardiff Road  
Newport  
South Wales  
NP10 8QQ

REC'D 29 OCT 1999

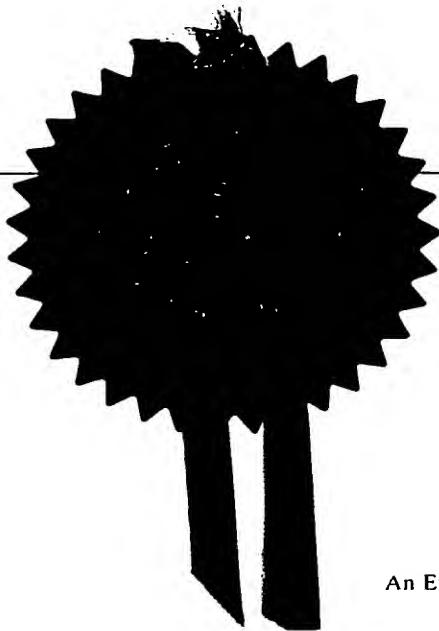
WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

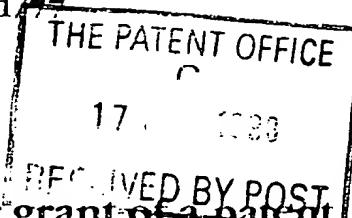
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed *Andrew George*  
Dated 11 October 1999

**THIS PAGE BLANK (USPTO)**

---



The Patent Office

Cardiff Road  
Newport  
Gwent NP9 1RH(See the notes on the back of this form. You can also get  
an explanatory leaflet from the Patent Office to help  
you fill in this form)

1. Your reference

474MCE98

2. Patent application number

(The Patent Office will fill in this part)

17 SEP 1998

9820163.5

3. Full name, address and postcode of the or of
- 
- each applicant (
- underline all surnames*
- )

SENTEC LTD  
TERRINGTON HOUSE  
13-15 HILLS ROAD  
CAMBRIDGE  
CB2 1GE

7353733002

Patents ADP number (*if you know it*)If the applicant is a corporate body, give the  
country/state of its incorporation

4. Title of the invention

MICRO-FABRICATED CODED LABELS, READING SYSTEMS AND  
THEIR APPLICATIONS

5. Name of your agent (
- if you have one*
- )

MR A. HOWE

*"Address for service" in the United Kingdom  
to which all correspondence should be sent  
(including the postcode)*

SENTEC LTD  
TERRINGTON HOUSE  
13-15 HILLS ROAD  
CAMBRIDGE CB2 1GE

Patents ADP number (*if you know it*)

7464621001

6. If you are declaring priority from one or more
- 
- earlier patent applications, give the country
- 
- and the date of filing of the or of each of these
- 
- earlier applications and (
- if you know it*
- ) the or
- 
- each application number

Country

Priority application number  
(*if you know it*)Date of filing  
(*day / month / year*)

NO

7. If this application is divided or otherwise
- 
- derived from an earlier UK application,
- 
- give the number and the filing date of
- 
- the earlier application

Number of earlier application

Date of filing  
(*day / month / year*)

NO

8. Is a statement of inventorship and of right
- 
- to grant of a patent required in support of
- 
- this request? (
- Answer 'Yes' if:*

YES

- a) *any applicant named in part 3 is not an inventor, or*
- b) *there is an inventor who is not named as an applicant, or*
- c) *any named applicant is a corporate body.*

*See note (d))*

9. Enter the number of sheets for any of the following items you are filing with this form.  
Do not count copies of the same document

Continuation sheets of this form

Description

5

*JP*

Claim(s)

1

Abstract

1

Drawing(s)

5 *M* 0527

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

1

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination  
(Patents Form 10/77)Any other documents  
(please specify)

NONE

11.

I/We request the grant of a patent on the basis of this application.

Signature

*MR A HOWE*

Date

15/9/98

12. Name and daytime telephone number of person to contact in the United Kingdom

01223 303800

MR ANDREW HOWE

**Warning**

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

**Notes**

- a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- b) Write your answers in capital letters using black ink or you may type them.
- c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- d) If you have answered 'Yes' Patents Form 7/77 will need to be filed. ✓
- e) Once you have filled in the form you must remember to sign and date it.
- f) For details of the fee and ways to pay please contact the Patent Office.

## **Micro-fabricated coded labels, reading systems and their applications**

This invention relates to micro-fabricated tags, methods for making them, reading them and using them.

5

### **Background and existing art**

Massively parallel bioassay tests are the enabling techniques that have made the majority of recent advances in genetics, screening and drug discovery possible. Thousands or millions of 10 tests that previously were carried out one by one are now combined into a single experiment yielding thousands or millions of results. The key to this process has been the development of techniques that allow the results of the many different tests to be separated from each other.

Currently there are a limited number of these techniques, all are costly to use, and none is 15 universally applicable. The techniques consist of labelling each of the constituent experiments in a manner that can be read after the experiment has completed. Labels used at present include the position of the experiment on the surface of a test chip and the fluorescent spectrum of a particle to which the experiment is bound.

20 The present market is dominated by US companies. Affymetrix markets a system called the GeneChip probe array. This is a DNA sequence testing chip, where tens of thousands of different DNA probes are located at known points on a large 2D array. Standard DNA hybridisation techniques are used in a chamber above the chip, and the test results are read out optically by the positions of fluorescent dots on the array. Some disadvantages are:

25

- High cost. A single GeneChip is very expensive, because the fabrication process is non-standard and highly complex, and the chips are in great demand. The readers are expensive with complex imaging optics.
- Single use. Once used, Affymetrix recommend that the GeneChip ( $12.5 \times 12.5 \text{ mm}^2$ ) is

30 thrown away.

- Lack of flexibility. Only DNA binding sites can be produced on the array.
- Lack of variety. There are only a handful of different chips at present. All the tests have to be designed by the chip maker, making it impossible to add new tests to an existing system.

35

Luminex Corporation's FlowMetrix system makes use of coded microspheres, 6.5  $\mu\text{m}$  in diameter. Each bead incorporates red and orange fluorophores to make up the code. Eight different intensities are possible, allowing 64 different bead types. A green fluorescent marker is used for the probes. The disadvantages of this system are:

5

- Relatively small number of codes – unsuitable for DNA probes
- Multi-wavelength optics required
- Systems are based around expensive (\$100,000) multi-purpose flow cytometers

10 This invention combines the advantages of the Affymetrix GeneChip (~10,000 independent tests at once) and the Luminex FlowMetrix system (flexible, customisable test panels, real-time test results, low-cost consumables). However, the cost of this system is likely to be substantially lower, because of the relatively simple nature of the code readout system. This opens up the possibility of the widespread use of readers in hospitals and doctors' surgeries,

15 for rapid screening purposes.

This invention describes a system for carrying out massively parallel multiple bioassay tests in a low-cost, fast and convenient manner. The scheme involves making a suspension containing many thousands of different types of micro-machined coded labels (micro-labels),  
20 each code carrying a different biochemical test. In one implementation, a novel reader system will draw through thousands of micro-labels per second, reading both the code and the result of the test. In this case, the code will be in the form of a transmission optical bar code, whilst the test result might typically be measured by the degree of fluorescence, or a colour change.

25

A specific embodiment of the invention will now be described by way of example with reference to the accompanying drawings in which:

Figure 1. Linear micro-label

30

Figure 2. How fluorescent markers become attached to micro-labels during bio-assay test

Figure 3. Silicon-on-Insulator-based label fabrication process

35

Figure 4. Schematic of linear label reading system

Figure 5. 2D labels

### Description of embodiment

5

This embodiment has three main components

- Micro-miniature coded labels (micro-labels) shown in Figure 1
- Fluid handling system to allow rapid, serial reading of the micro-labels
- 10 • Optics and signal processing to read the micro-label code and the amount of fluorescence (Figure 4)

In this embodiment, the micro-labels consist of micro-machined miniature optical bar codes, made from silicon, using conventional VLSI techniques, with minimum feature sizes of around 2  $\mu\text{m}$ . To enable accurate reading of the smallest label, they are made as thin strips with holes cut away to encode the data. Each micro-label is about 100  $\mu\text{m}$  long by 10  $\mu\text{m}$  wide by 1 micron thick, and is capable of storing up to 100,000 different codes. This is shown in Figure 1. Around 10 million such micro-labels can be fabricated on a single 6-inch diameter substrate, using relatively conventional optical lithography. A number of low cost fabrication methods are possible, borrowing ideas from industries such as amorphous silicon solar cell and LCD display fabrication. Figure 3 shows a fabrication process based on Silicon-on-Insulator material.

Each code will uniquely identify a unique biochemical test, or probe. The probe is incorporated as part of the micro-label using well known techniques to coat the label with a particular DNA sequence, protein or antibody, which will bind to a specific target. The sample under test is labelled with a fluorescent marker, and incubated with a suspension of a mixture of the coded micro-labels. When the labelled target molecules bind to the antibody or DNA on a micro-label, the micro-label then becomes fluorescent, leading to a suspension

---

30 of labels, some of which will have fluorescent groups attached (Figure 2).

A typical application might use a suspension of probes for a number of different antibodies (e.g. hepatitis, HIV). A reading system would take a drop of blood from a patient, label it with fluorescent marker, and incubate this with the probe suspension for a few minutes. The 35 suspension would then be fed through a microfluidic detector system.

This will be a design that induces the micro-labels to flow down the centre of the tube in the central reading zone. There are two possible approaches to this – one is based on microfluidics alone, the other combines this with some magnetic material on the label and suitable coils and magnets to orient and position the label. In the second case, the label can be aligned with the flow direction by applying an axial magnetic field. This will enable the micron-scale bar code data to be read rapidly with very simple optics and signal processing.

The pattern of holes on the label will be read by arranging for the label to intersect two orthogonal focused beams of light. The holes in the label will modulate the transmitted intensity as the label passes through, generating a serial stream of information that can be analysed in the same way as a conventional bar code. Simultaneously, the degree of fluorescence will be measured using a separate detector, and this will be correlated with the code on the label (Figure 4). High N.A. optics are needed to achieve the desired resolution. Even so, the optics and fluid handling required will be substantially simpler than in a conventional flow cytometer, where both scattering and multi-wavelength fluorescence analysis are normally used.

Once sufficient micro-labels have been read, the reader calculates the results of all the tests. For example, with blood samples, this would be a list of the disease strains found. In practice, each probe suspension would contain many copies of each of the desired tests to ensure a robust result. Washing and separating the blood from the micro-labels should be unnecessary because the micro-labels will be used to gate the fluorescence signals. Only very small amounts of sample and reagents are required, reducing the operating costs of the system.

- The commercial products can be grouped into a number of categories:
- 25     • Suspensions of single-code micro-labels, prepared for probe attachment
  - Suspensions of single-code micro-labels, with attached antibody, protein or DNA probe
  - “Test-panels” of a large number of differently-coded micro-labels each with a unique probe
  - 30     • Reading systems such as a desktop reader

#### **Alternative features and embodiments**

- 35     The embodiment above discusses a linear label with a code read by optical transmission. Alternative linear designs without holes in the label include:

- stripes of different (spectral) reflectivity or colour
- stripes of dielectric layers of one or more different thicknesses
- gratings with different pitches

5

An alternative is to use a 2D pattern, and fabricate labels which are closer to being square or rectangular, rather than linear. These labels require a different reading system, based on filtering or spinning out the label suspension onto a flat substrate. Labels incorporating magnetic material can use magnetic separation. This is useful if the sample being tested 10 contains solid matter of similar size to the labels which could contaminate the results. The labels can then be read using a standard microscope system, either in transmission (for labels with holes) or with epi-illumination. This has the advantage of defining the focal plane accurately, at the expense of removing the transport mechanism for moving labels through the reader system.

15

Coding schemes similar to conventional 2D barcodes can be used. The outline of the label can be used to give orientation information. Some examples of different coding arrangements are given below.

20

Most codes are based around a grid of possible sites for holes on the label. The orientation is determined by a cut-out on the outside of the label. If the minimum feature size and the placement accuracy are both  $f$ , the grid has a pitch of  $f$ , and a selection rule is used which prevents holes from being placed closer than  $2f$ . For example, using a  $6 \times 6$  grid with a pitch of  $2.5 \mu\text{m}$ , the label with cut-out is  $22.5 \times 20 \mu\text{m}$ , and the number of codes is in excess of  $10^5$  25 (Figure 5a).

If the manufacturing process can tolerate *placement* of the holes to a higher precision than the minimum feature size (e.g. placement to  $0.83 \mu\text{m}$ , with a minimum feature size of  $2.5 \mu\text{m}$ ), then higher data densities can be achieved: for example,  $10^5$  codes can be produced on a grid

30

of  $12 \times 12$  sites at a pitch of  $0.83 \mu\text{m}$ , with a selection rule preventing sites which are closer than  $5 \mu\text{m}$  from being occupied. This gives a label with cut-out which is  $19 \times 16.5 \mu\text{m}$  (Figure 5b).

35

Figure 5c shows a very simple, intuitive 2D coding scheme. There are 5 rows, each with ten possible positions for a single hole in each row, at a pitch of  $1 \mu\text{m}$ . This gives a total of  $10^5$  codes. The orientation of the label is determined by a cut-out on the edge.

**CLAIMS**

1. Small labels held in suspension incorporating a spatially varying pattern for identification.  
5  
2. Optical reader for reading codes on labels in 1
3. Labels where pattern is a barcode
- 10 4. Labels where pattern is linear barcode
5. Labels in 1 using transmission optics
6. Labels in 1 incorporating biochemical test
- 15 7. As in 6, result indicated by fluorescence
8. Labels in 6 with reader (2) plus method for interrogating result of test
- 20 9. Method of making labels 1 by lithographic process
10. Method of bio assay
11. Fluid dynamic method of aligning labels with fluid flow
- 25 12. Magnetic method of aligning particles with fluid flow
13. Label as in 1 where pattern is a diffraction grating

---

- 30 14. Method of filtering out labels and reading codes on surface of filter
15. Method of magnetically separating particles

## **ABSTRACT**

This invention relates to a micro-machined label incorporating a spatially varying pattern, capable of storing many thousands of codes, primarily for use in massively parallel bio-assay 5 applications. The invention describes methods for making the labels, reading them, and using them for bio-assay purposes.

10

Sentec Ltd check box:

15

Pages of text	: 5
Pages of claims	: 1
Pages of abstract	: 1 (this one)
Pages of figures	: 5

20

### **Initial Application**

#### **INVENTION TITLE:**

25

**Micro-fabricated coded labels, reading systems and their applications**

30

---

35

THIS PAGE BLANK (USPTO)

---

FIGURES

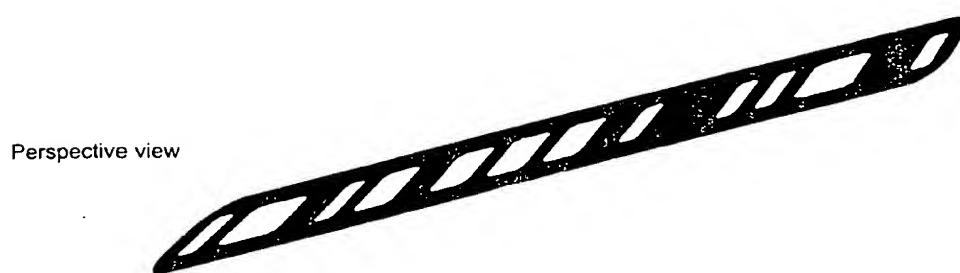
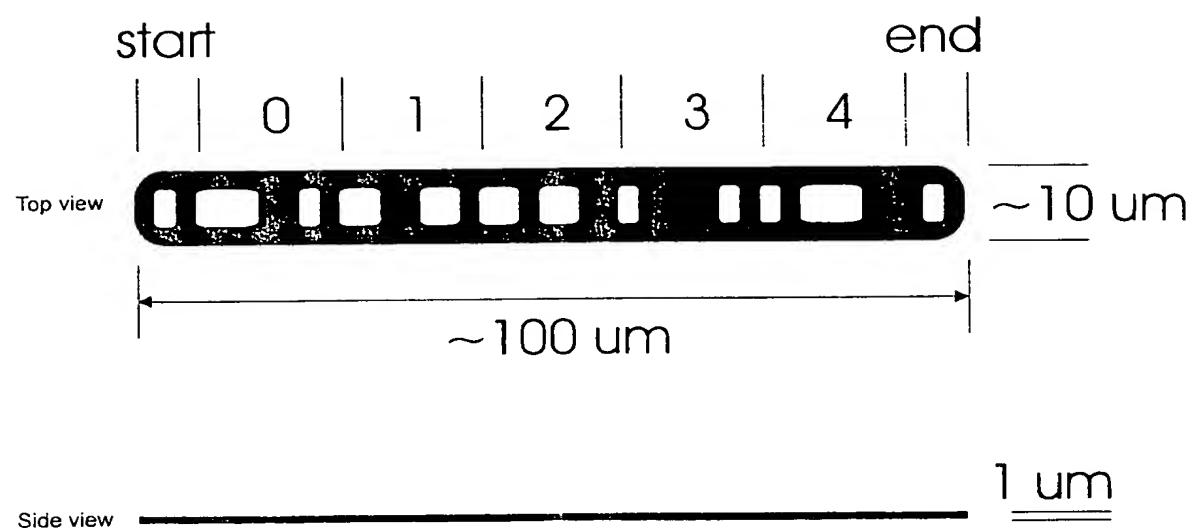


Figure 1.

**THIS PAGE BLANK (USPTO)**

---

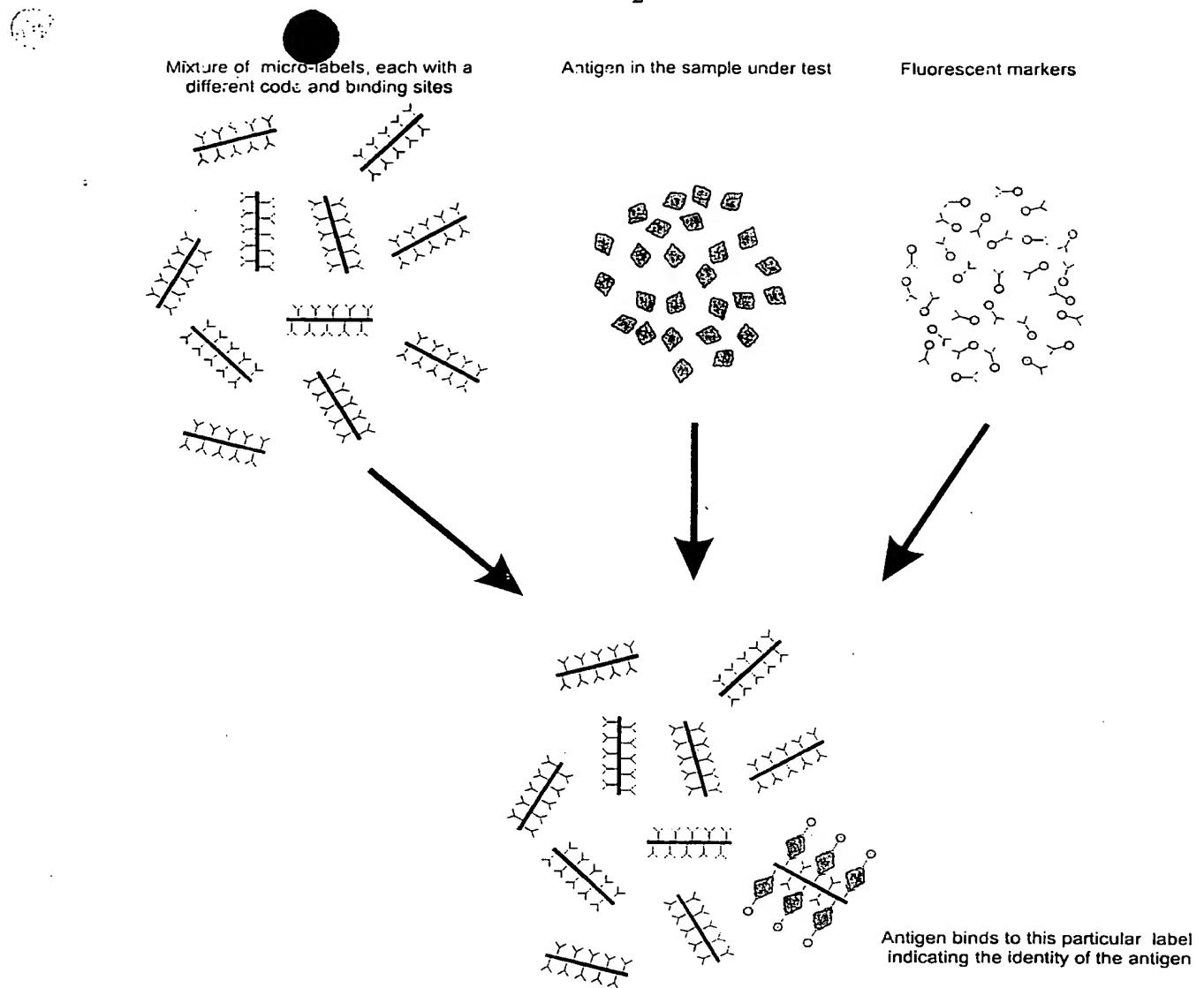


Figure 2.

**THIS PAGE BLANK (USPTO)**

---

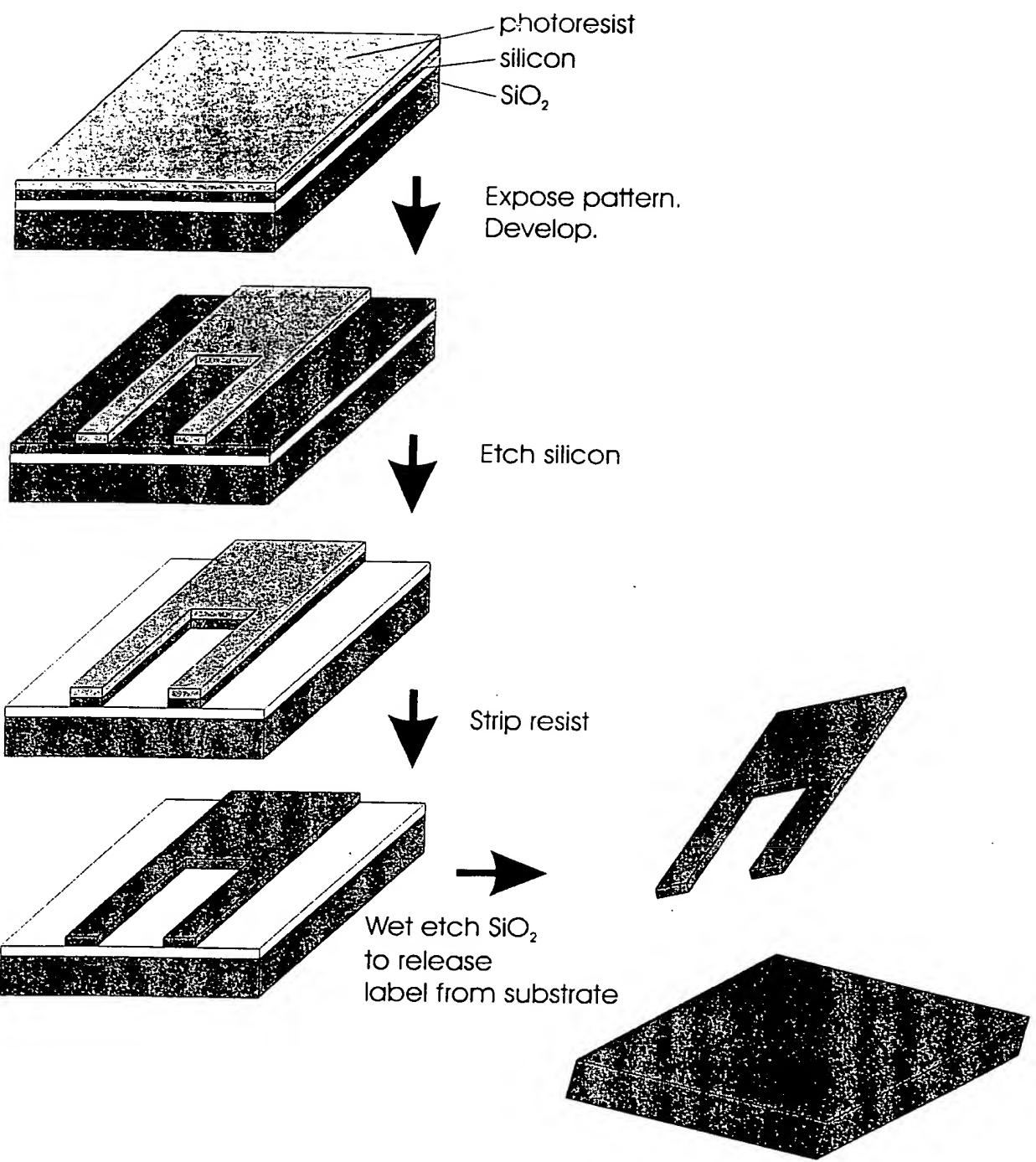


Figure 3.

**THIS PAGE BLANK (USPTO)**

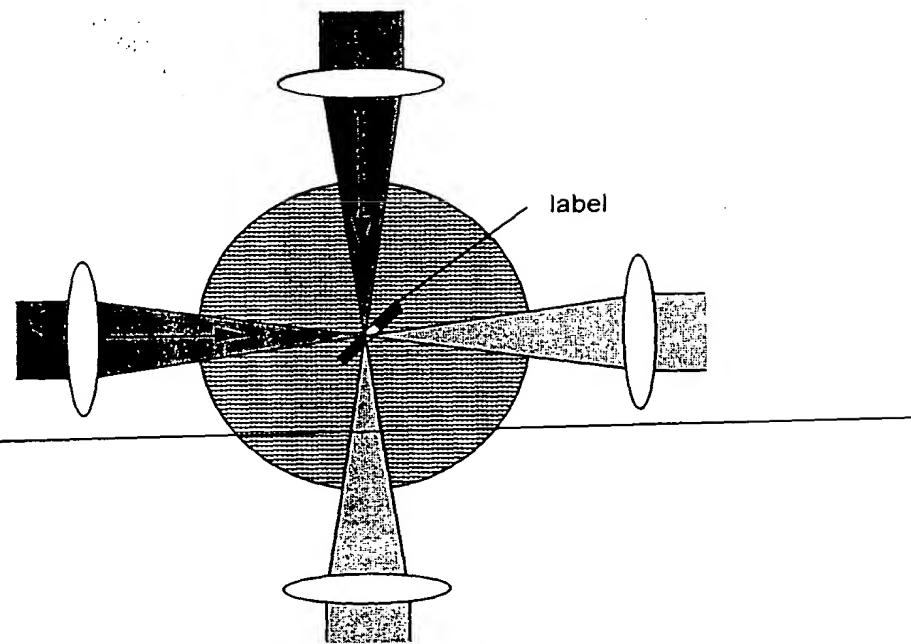
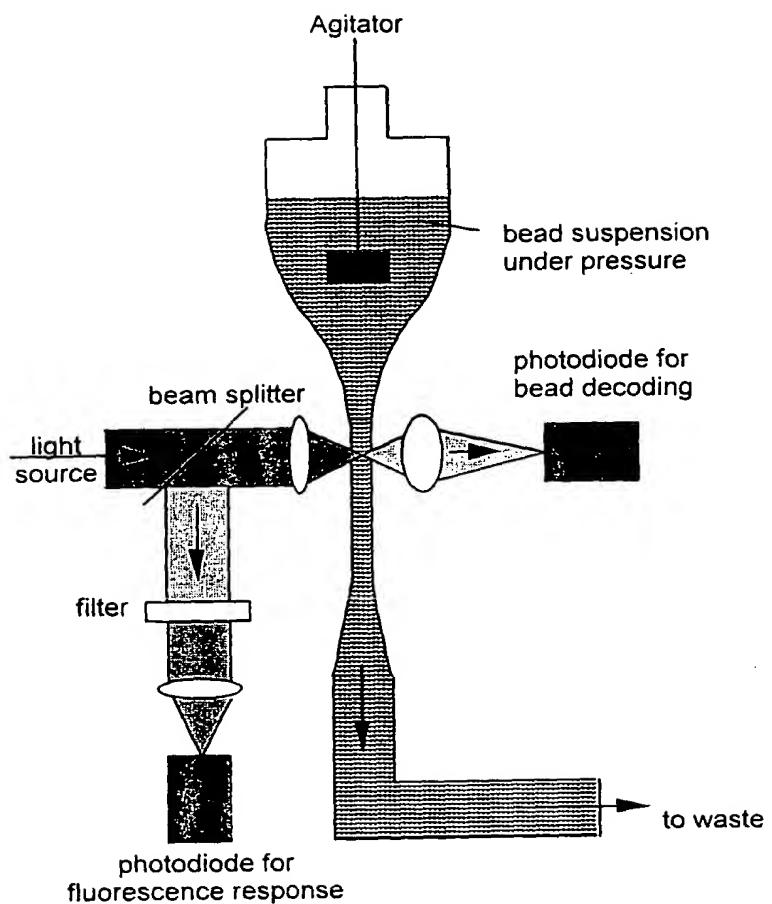
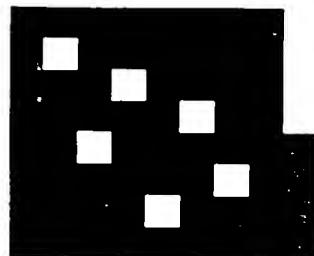


Figure 4.

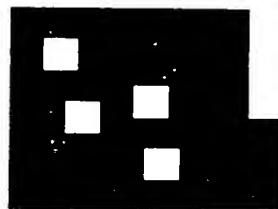
**THIS PAGE BLANK (USPTO)**

---

a. 2.5 um grid



b. 0.83 um grid



c. 5 rows  
1um increment

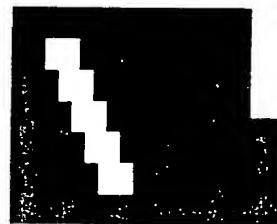


Figure 5.

PET/ISB/CS/10719

2019/09/07

Sentec AD

THIS PAGE BLANK (USPTO)